THE PROPHYLACTIC TREATMENT OF RHEUMATIC FEVER BY SULFANILAMIDE

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RHEUMATIC fever is generally recognized as an acute disease with a great variety of clinical manifestations, which frequently recurs again and again in the same patient and may result in permanent organic heart disease. While rheumatic fever presents the clinical picture of an infectious disease, no bacteriological organism or virus has yet been consistently cultivated from the acute lesions, nor has the causative agent been directly established by other means. However, in the past ten or fifteen years a great deal of evidence has accumulated to show that acute attacks of rheumatic fever are usually preceded by some infection with the beta hemolytic streptococcus, such as acute pharyngitis or tonsillitis, or scarlet fever. Such an infection is usually followed by a latent period of one, two, or three weeks before the rheumatic episode begins. During the attack of rheumatic fever the antistreptolysin titer of the blood rises, even though the hemolytic streptococcus can no longer be cultivated from the throat of the patient, and this fact, also, has been considered to show some specific relationship between the antecedent beta hemolytic streptococcal infection and the period of rheumatic activity.

At present, there is no known specific cure for rheumatic fever. None of the sulfonamide drugs thus far developed have appeared to be of any value in combatting the acute attack of rheumatic fever, in contrast to their usefulness in lobar pneumonia, for example. The conservative measures of administering salicylates and keeping the patient at rest have only limited usefulness; they do not prevent renewed attacks of rheumatic fever, and they do not prevent the development of heart disease.

Since the first attack of acute rheumatic fever is seldom fatal, and rarely damages the heart severely enough to permanently impair its normal function, it seemed to me that the most important thing to be

done if possible was to prevent subsequent recurrences, once rheumatic fever had proclaimed itself, by preventing the antecedent beta hemolytic streptococcal infections. In 1935 and 1936 reports were published abroad concerning the protective effect of sulfanilamide in experimentally induced beta hemolytic streptococcus infections in mice. When the drug was administered before the streptococcus had had an opportunity to invade and multiply in the tissues, doses very much smaller than the usual curative dose proved effective prophylactically. These experiments made it seem worth while to undertake a carefully controlled study of the effect of administering small daily doses of sulfanilamide to patients recently recovered from acute rheumatic fever. By giving such prophylactic doses continuously over a long period of time we hoped that acute hemolytic streptococcal infections could be prevented in these rheumatic subjects, and that recrudescences of rheumatic fever would therefore not occur.

We embarked upon such a study in September 1936; the details of our observations during the first four years have already been published.[1, 2] In brief, we selected to receive the prophylactic treatment a group of adolescents and young adults, each of whom had had acute rheumatic fever within three years of entering the study, and observed other patients with similar histories as a control group. The patients were all ambulatory and in the quiescent phase of their disease; they were carefully followed in the Cardiac Clinic of the Department of Medicine in the Johns Hopkins Hospital. All had had one or more attacks of polyarthritis or carditis or both. The patients varied in age from seven to thirty-seven years, the great majority being between fourteen and twenty-six years of age. Sixty-nine per cent had chronic rheumatic endocarditis, 33 per cent had definite cardiac enlargement, but very few had definite reduction of the functional cardiac capacity. The treated and control groups were matched as closely as possible as to age, sex, race, history of rheumatic fever, and cardiac lesions.

The treated group were given sulfanilamide daily from October or November until June. The first year we gave 1 gram, or 15 grains a day in three 5 grain doses. The results that year were entirely satisfactory, but because we believed it was difficult for young people away from home, at school or at work, to remember to take the noon dose, the next year we altered the schedule to two 10 grain doses taken morning

TABLE I

COMPARISON OF THE INCIDENCE OF POSITIVE PHARYNGEAL CULTURES IN THE TREATED AND CONTROL GROUPS

Season	*Treated Group During Sulfanilamide Season*			*Control Group During Control Season*		
	Total Number of Throat Cultures	*Throat Cultures Positive for Beta Hemolytic Streptococci*		*Total Number of Throat Cultures*	*Throat Cultures Postive for Beta Hemolytic Streptococci*	
		No.	*%*		*No.*	*%*
1936-1937 and 1937-1938	166	8	4.7	71	10	14.1
1938-1939	136	7	5.1	100	12	12.0
1939-1940	198	5	2.5	165	19	11.5
Total for 1936-1940	500	20	4.0	336	41	12.2

and night, or approximately 1.3 grams a day. With rare exceptions we gave the same dosage to everyone, regardless of body weight. Two or three of the youngest ones received only a gram a day for a number of months.

In the original study, fifty-five patients were treated prophylactically over a total of seventy-nine person-seasons, while sixty-seven control patients, thirty-two of whom had been treated in previous seasons, were observed over a total of 150 person-seasons. The results, both as regards inhibiting the beta hemolytic streptococcus and preventing rheumatic recrudescences were strikingly favorable. At each visit the pharynx of both treated and control patients had been swabbed in two different areas, the two swabs being immediately dropped into tubes of broth and promptly carried to the laboratory for culture. Twelve and two-tenths per cent of 336 such cultures made on the patients in the control group were positive for beta hemolytic streptococci. This incidence agrees well with that found in two studies on the carrier rate of the beta hemolytic streptococcus among normal persons living in Baltimore. Bourn, Carpenter and McComb[3] reported 10.4 per cent positive cultures among 2,812 persons, and Long and Bliss[4] found 10 per cent and 13 per cent positive pharyngeal cultures in two smaller groups of patients. In contrast, only 4 per cent of 500 pharyngeal cultures obtained from our treated group of patients were positive for the beta hemolytic

TABLE II

OCCURRENCE OF MAJOR RHEUMATIC EPISODES IN THE PROPHYLACTICALLY TREATED AND CONTROL GROUPS OF PATIENTS

Group	*Person-Seasons*	*Major Episodes*	
		Number	*Percentage*
Sulfanilamide	79	0	0
Control	150	15	10.0
Total	229	15	6.6

streptococcus. This threefold difference was consistently noted throughout each season while sulfanilamide was administered.

The incidence of positive cultures in the treated group rose during the summer months while sulfanilamide was not given from 4 per cent to 18 per cent. This shows that the treated group was not inherently less susceptible to harboring the beta hemolytic streptococcus. It was also found that colonies of the hemolytic streptococcus were several times more numerous in the positive cultures of untreated than of treated patients.

None of the patients receiving sulfanilamide prophylactically suffered from any acute beta hemolytic streptococcus infection during the period of treatment. Two of the control patients had acute beta hemolytic streptococcus infections which were not followed by rheumatic recrudescences, and sore throats or markedly positive cultures or both preceded major rheumatic episodes in six of the ten control patients observed in the prodromal period. A seventh patient had many positive cultures during the rheumatic recrudescence but there was no sore throat and throat culture was negative at the onset.

During the four year study, not a single major attack of rheumatic fever occurred in any patient while taking sulfanilamide prophylactically. In contrast, fifteen major rheumatic episodes were observed among control patients during the same period, and five more control patients suffered from acute illnesses which might have been rheumatic in character. One boy who had taken sulfanilamide faithfully from October to June developed acute rheumatic fever in August, while he was not receiving treatment.

TABLE III

DISTRIBUTION OF MAJOR RHEUMATIC EPISODES BETWEEN TWO SUBDIVISIONS OF CONTROL GROUP

	Person-Seasons	*Major Episodes*	
		Number	*Percentage*
A. Had sulfanilamide other seasons	84.5	8	9.4
B. Never had sulfanilamide	65.5	7	10.7
Total control group	150	15	10.0

Thus 10 per cent of the control group had recrudescences, while none of the treated group were affected. It apparently made no difference whether prophylactic sulfanilamide had been taken at some previous period, for the recrudescences observed in the control group were about equally divided between those controls who had had sulfanilamide in years past and those who had never received the drug.

The difference in the number of recrudescences between the treated and control group was great enough to be statistically significant. It appeared, then, that we had found real evidence to show that small daily doses of sulfanilamide have a prophylactic effect in preventing recurrent attacks of acute rheumatic fever. Toxic reactions, which I shall discuss presently, were negligible in our series.

Today I want to describe several interesting observations we have made during the year and a half since our four year study was completed, to correlate our results with those of others working in the same field, and in particular, to discuss a number of questions which arise in connection with this new approach to the treatment of rheumatic fever. In the season of 1940-1941 we accepted prophylactic sulfanilamide as a valuable medical procedure in the management of rheumatic patients, administering it to all of the patients in the previous study who desired to continue to take it as well as to any suitable new patients referred to us. In order to undertake other studies related to rheumatic patients, we gave up the burden of following a formal control group, although many rheumatic patients not on sulfanilamide therapy continued to come to the Cardiac Clinic. Of the twenty-five patients who received the drug prophylactically during the last year of our study, twenty-one

elected to continue it in 1940-41, and fourteen of them are still taking sulfanilamide this winter (1941-1942). We have therefore had the opportunity of observing nineteen patients who have taken sulfanilamide for three or more years. Of these, eleven have taken the drug for three years, four patients for four years, three for five years, and one boy who was in our first group, is now taking sulfanilamide for the sixth year.

S. R. entered the study in October 1936, at the age of seventeen, shortly after his fourth attack of rheumatic fever. He was the one who had an acute attack in August, after his second season of sulfanilamide, while he was not taking the drug. Since that recrudescence he has insisted upon taking the drug summer and winter, so that for the last four years he has never been without it. He had mitral stenosis and aortic insufficiency upon entering the study, without cardiac decompensation. Under treatment he has had no further acute rheumatic fever, his cardiac lesion has remained stationary, and he has worked hard at a factory job while attending night school to make up for the schooling he lost during years in bed. There is no evidence that the continuous use of sulfanilamide has undesirably affected either his mental or physical state.

The others who have taken sulfanilamide for long periods of time are in vigorous physical condition, have seemed unusually free from minor illnesses and most have been able to work hard or attend school or both, with the exceptions to be noted presently. There is no evidence of loss of weight over the period of years, and minor toxic reactions at the time of restarting the drug in the autumn have been notably absent. Several of these patients in addition to the boy mentioned have taken the drug summer and winter for two or more years. In view of our favorable experience, it now seems wiser to administer the drug the year around rather than giving the patient a summer vacation, since rheumatic recurrences may come at any season. This procedure, from a practical point of view, greatly lessens the work which is necessary when all the patients need to be started on the drug each fall.

We have had the first two rheumatic recrudescences in treated cases observed by us in the course of six years, one last winter and one this December.

G. B., a white girl of sixteen years, was admitted to the study in October, 1938, six months after her third attack of acute rheumatic

fever. She received prophylactic sulfanilamide for two seasons uneventfully, while she worked as attendant on one of the children's wards in the hospital. In October, 1940, she started to take sulfanilamide for the third season. She was married in December and took a factory job on the night shift. She found these new adjustments difficult and was fearful and under nervous strain. During the winter she had two slight colds without acute sore throats; the pharyngeal culture and sedimentation rate* were always normal at her regular clinic visits. On March 28 she was found to have well marked chorea and was admitted to the ward, where she remained seven weeks. At no time did she have fever, leucocytosis, elevation of the sedimentation rate, electrocardiographic changes or clinical evidence of acute rheumatic fever apart from the chorea. The beta hemolytic streptococcus was never cultivated from her pharynx. Prophylactic sulfanilamide was resumed three weeks before leaving the hospital without incident. She is taking it again this winter.

Here, then, is our first instance of major recrudescence in a treated patient. In this case the recurrence took the form of pure chorea, without any evidence of preceding beta hemolytic streptococcal infection. In view of the uncertainty of the etiological factors contributing to the appearance of chorea, we can only speculate as to whether sulfanilamide prophylaxis will prove to be effective in this particular variant of the rheumatic state.

This winter, however, we have had a definite flare-up of acute rheumatic fever occurring in a patient who was taking prophylactic sulfanilamide for the fourth season.

R. H., a negro boy of seventeen years, entered the study in January, 1939, ten days after discharge from the hospital ward where he had been for three months with his sixth attack of rheumatic fever in six years. He was given prophylactic sulfanilamide, which he took fairly conscientiously. Although he sometimes admitted skipping an occasional dose, he said he never omitted the drug for a whole day. He had been recently working as a junk man. On December 13, 1941, he was out all day in a sleet storm and became chilled and soaked to the skin. December 16 he had a pain in his back, felt badly and went to bed. Three days later his left knee began to hurt. He came to the Cardiac Clinic the next day, where he was found to have fever, tachycardia and a

* Sedimentation rates were done by the Wintrobe method.

swollen fluctuant left knee joint. He was admitted to the hospital. There was no story of sore throat and on admission his pharyngeal culture was negative for beta hemolytic streptococcus, although a few colonies had been present several weeks before. His temperature reached 104.5° the day of admission, his sedimentation rate was 26 mm. in an hour. On acetylsalicylic acid his temperature fell to normal in thirty-six hours, his pulse rate subsided. No further joints became involved, his sedimentation rate became normal and remained so at the end of the first week. Serial electrocardiograms showed slight prolongation of the P-R interval on the fifth day, which promptly disappeared. Prophylactic sulfanilamide was resumed twenty days after admission and two days later he was discharged. He has been resting at home since, feeling perfectly well. His sedimentation rate has remained normal.

Here, then is a definite instance of failure of sulfanilamide to protect. Although one can hardly expect a perfect record from any form of therapy, it is worth pointing out that this attack was apparently mild, and of brief duration.

In addition to the patients who first started sulfanilamide as part of the study, we have given it to ten or twelve other patients in the course of the past year and a half. Since they began the drug at varying times of year, we have not added them to the patients of the original group who have received a total of 114 patient-seasons of sulfanilamide treatment.

It is now our custom to start giving prophylactic sulfanilamide to convalescent rheumatic patients a few days or a week before discharge from the hospital. We think this important because several patients, who were discharged from the hospital with negative pharyngeal cultures, returned to the Cardiac Clinic two or three weeks later with a heavy predominance of beta hemolytic streptococci in the cultures then taken, indicating prompt re-invasion by that organism as soon as the patient returned to his home surroundings. We have had no difficulty in administering sulfanilamide to patients who are afebrile and asymptomatic after salicylates have been withdrawn, and we have not found it necessary to wait for the sedimentation rate to return to normal.

Let me now refer to other interesting studies which have been carried out on this subject. In the same year that we began our observations, Coburn and Moore[5] started to give sulfanilamide prophylactically to several groups of rheumatic children both in a convalescent home and

in regular and special schools in New York City. In 1940 they reported[6] that only one out of 184 subjects thus treated had developed rheumatic fever. In 1939, they observed 129 untreated adolescents and young adults as a control group and noted a 20 per cent incidence of rheumatic attacks, while in 1938 and 1939, 35 per cent of a smaller untreated group of children suffered from recrudescences. They also noted a striking difference between treated and control groups in the presence of the hemolytic streptococcus and streptococcal infections.

In the last two years several investigations of the same question have been undertaken, most of which are still in the process of completion. This is most encouraging, for it is of the greatest importance that the use of prophylactic sulfanilamide be studied under many conditions of age, climate, environment and general hygiene. Last winter, Kuttner[7] divided the convalescent rheumatic children at Irvington House into two equal groups, and gave sulfanilamide prophylactically to one group. None of the treated group had a rheumatic recrudescence and only one had streptococcal pharyngitis, while 30 of the 54 untreated children developed streptococcal pharyngitis and 14 of these subsequently developed clinical rheumatic recurrences. Four others showed laboratory evidence of rheumatic reactivation. This study, which Kuttner has already presented before the Brooklyn Academy of Pediatrics and which is soon to be published, is most convincing, for both treated and control groups were exposed to the same environment with little outside contact, and all were equally exposed to beta hemolytic streptococcal carriers within the convalescent home itself.

In the Bellevue Childrens' and Adolescents' Clinics[8] a large group of children have thus far been treated for 150 patient-seasons with no recurrences except in three far advanced cases. Chandler and Taussig[9] in Baltimore have had no recurrences to date among rheumatic children observed for 41 patient-seasons, and Roberts[10] in Philadelphia has had equal success with a similar group. Stowell and Button[11] in New York City found that sulfanilamide appeared effective in protecting against recurrences of rheumatic fever, but reported unfavorably upon the toxicity of the drug, with one death from agranulocytosis.

Here is a summary of the work done by the groups mentioned, three of whom have most kindly permitted me to refer to their studies while they are yet in progress (Table IV). Fortunately, sulfanilamide was the drug used throughout; no other sulfonamide drug has thus far been

TABLE IV

SUMMARY OF STUDIES ON THE USE OF PROPHYLACTIC SULFANILAMIDE IN RHEUMATIC FEVER

Author	*Type of Patient*	*Age of Patient*	*Years of Study*	*Daily Dose of Sulfanilamide*	*No. of Patient Seasons*	*Results*	*Toxic Effects*
Thomas et al.	Clinic	8-37	1936-1942	Grams 1.0-1.3	114	Excellent	Few and Mild
Coburn and Moore	Convalescent Home and Clinic	6-14	1936-1940	2.0-3.0	189	Excellent	10% None Serious
Stowell and Button	Clinic	11 (Average)	1940-1941	1.5-2.0	46	Fair	One Death
Chandler and Taussig*	Clinic	6-16 (One of 20)	1939-1942	0.6-1.7	41	Excellent	Few and Mild
Kuttner*	Convalescent Home	7-15	1940-1942	1.0-2.0	108	Excellent	15% None Serious
Bellevue* Childrens' and Adolescents' Clinics	Clinic	8-17	1939-1942	1.0-2 3	150	Excellent	Mild; None Sufficient to Stop Drug
					Total (648)		

* To be published.

tried in the prophylaxis of rheumatic fever to my knowledge. Several investigators have considered testing the value of sulfadiazine in this regard, but at present it would be very expensive to use it over months and years. Table IV shows that several hundred children and young adults have received sulfanilamide prophylactically for a total of 648 patient-seasons during the past six years. Thus far, only six have had rheumatic recrudescences, an incidence of less than one per cent. One of these recrudescences was pure chorea and three occurred in advanced cases of the chronic type. Recrudescences have been noted in from 10 to 35 per cent of the control patients, the incidence varying with age, from group to group and from year to year. Among the treated group we might therefore have expected at least 130 attacks (an incidence of 20 per cent) rather than six, if sulfanilamide were ineffective. By grouping together these studies the results mount up into an impressive body of evidence in favor of this method of treatment.

Although on casual inspection the dosage administered by the different groups seem similar, some groups have used double and almost triple the daily dose used by others. Thus throughout the first year we gave only 1.0 gram a day to adolescents and adults, and since then have given no more than 1.3 grams a day. Chandler and Taussig[9] gave a similar small dose. Coburn and Moore,[5,6] on the other hand, gave 2 grams a day to small children, 3 grams a day to large children. Stowell and Button[11] gave 2 grams a day to all but the smallest children, those weighing under 55 lbs., which would be the six and seven year olds. The other two studies have used an intermediate dosage.

The concentration of sulfanilamide in the blood has been studied in each group and has been found to vary from 1.0 to 5.0 mgm. per cent. There is no theoretical basis for determining the minimal blood level which will provide adequate protection against invasion by the streptococcus. So far the amount of protection indicated by our clinical results and those of Chandler and Taussig, using small dosages, has been as great as that found in the groups where larger doses are used.

It is worth noting that these two "small dose" groups have had the least trouble with toxic reactions. In children, Chandler and Taussig observed transient rashes in three, mild gastrointestinal upsets in three, slight leucopenia in three. They have had no reactions severe enough to stop the drug permanently. All these mild symptoms appeared shortly after starting treatment, none appeared late in the course of treatment. Our experience has been with similar mild symptoms. We have not observed the transient anorexia and weight loss which Chandler and Taussig report as occasionally present after beginning the drug, and which Coburn and Moore mentioned in their first paper.

Only two patients in our group have stopped the drug on account of toxic reactions. One boy had urticaria and nausea and refused to continue taking it, although his symptoms were not serious. The second child, previously reported as reacting unfavorably to the drug, has since been able to take it and has done so for nearly a year.

N. S., a seven year old white boy, was started on prophylactic sulfanilamide, 0.9 gram a day, in January 1940, six months after his second attack of rheumatic fever. The day he first started the drug his leucocyte count was 19,150 for no obvious reason; three days later he had a cold and looked flushed, and on the seventh day the white blood cell count had fallen to 4,300 and he complained of fatigue. Segmented neutrophils

fell from 50 per cent to 28 per cent, while juvenile neutrophils rose from 5 per cent to 17 per cent. Sulfanilamide was stopped, and the leucocyte count gradually rose to 11,600 in the next eleven days.

Two more 0.3 gram tablets were administered, one at night and one the next morning. He again appeared flushed, so he was brought in and his leucocyte count found to be 14,200. The drug was stopped, and two days later he had 6,700 leucocytes with 38 per cent adult and 3 per cent juvenile neutrophils. The drug was discontinued for the year on account of the unstable leucocyte count, fatigue and flushing.

The next winter, in November 1940, he had his third attack of acute rheumatic fever and was in the hospital nearly three months. Toward the end of his stay in the hospital 0.3 gram of sulfanilamide was administered on two consecutive days. His leucocyte count remained unchanged around 11,000, but on the afternoon of the first day his temperature spiked to 101° for the first time in weeks, so the drug was once more discontinued. (A similar spike was observed a week later when he was not taking sulfanilamide.) In March 1941, after he had been out of the hospital a month, he was again cautiously started on sulfanilamide 0.25 gram a day in capsules. His leucocyte count was 7,700 and his polymorphonuclears 30 per cent, all adult forms, the day the medication was started. No significant change in total white cells occurred during three weeks; the neutrophils increased to 53 per cent. The dose was then increased to 0.5 gram a day. His count never fell below 5,000, and he now has taken 0.6 gram a day since August, feels well, and has a perfectly stable, normal leucocyte count.

Coburn and Moore[5,6] noted toxic symptoms in 10 per cent of the children under their care within a few days after starting medication. The patients who tolerated the drug for two weeks remained symptom-free thereafter. In the Bellevue Childrens' and Adolescents' Clinics,[8] no toxic symptoms serious enough to necessitate discontinuing the drug have been encountered. Kuttner,[7] on the other hand, has withdrawn the drug within five weeks of beginning treatment in 15 per cent of her patients on account of rash with or without fever, at times accompanied by abdominal pain, nausea and vomiting. She has also encountered leucopenia and decrease in the percentage of granulocytes.

Stowell and Button[11] observed toxic effects in 19 out of 46 patients treated prophylactically. In 25 per cent the drug was stopped permanently on this account. Persistent rash, fever, nausea and lowering

of the leucocyte count were the principal reactions. They also reported the first death from prophylactic sulfanilamide, due to agranulocytosis. A twelve year old boy had received 0.6 gram three times a day (or 1.8 grams a day) prophylactically for twenty-nine days when sore throat and fever developed. His leucocyte count was normal three days previously. Instead of being brought to the clinic according to instructions, a private physician treated him at home for two more days, during which time he received small amounts of the drug. On admission to the hospital he had ulcerative pharyngitis, high fever, 300 leucocytes per c. mm. of blood, with only 1 per cent polymorphonuclear cells. Blood culture was positive for staphylococcus and pneumococcus. He died on the fourth day after admission.

In discussing these undesirable reactions, let us consider nausea, rash and fever first, and then leucopenia and agranulocytosis. Nausea, fever and rash are disagreeable symptoms which are important in that they interfere with the prescribed treatment, but they do no serious harm to the patient. There is good evidence that they are more prevalent when large doses of the drug are given than when smaller doses are used. Stowell and Button noted two patients who developed rash on 1.8 grams a day which disappeared when the dose was lowered to 1.2 grams a day. I predict that few patients would need to stop the drug permanently on account of these symptoms if the smaller prophylactic dosage were used. Those patients who do show symptoms should stop the drug, resuming it after several weeks at a dose of 0.3 gram a day. This dose may gradually be increased to the desired total dose over several weeks. It may be that such graduated dosage administered to all patients beginning the drug would tend to eliminate toxic effects.

A number of us have observed a gradual lowering of the total leucocyte count during the first weeks of treatment, sometimes to levels between 2,500 and 4,500, with subsequent increase to normal without discontinuing the drug. Other authors have commented upon this as a benign and fairly common occurrence. The granulocytes may not be depressed, or may fall to 25 or 30 per cent. Since agranulocytosis does rarely occur, however, following sulfanilamide administration, the development of leucopenia must be watched for with the greatest care so that the drug may be discontinued whenever an abrupt decrease in leucocytes occurs.

Since Stowell and Button's[11] report of a case of fatal agranulocytosis,

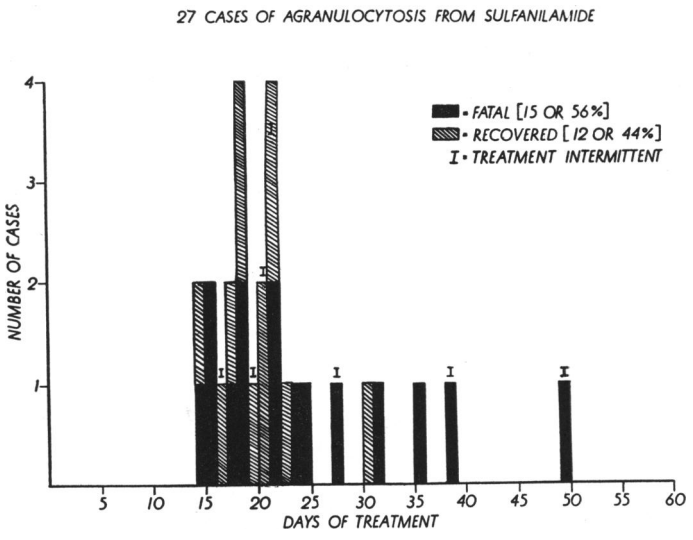

Fig. 1—For the cases charted in Figure 1 see references 11-36, i.. the order of length of treatment, with two exceptions. Garvin[18] cites two cases, one treated 14 days, the other 17 days. Stowell and Button's case[11] was treated 31 days.

I have reviewed all the available reports of agranulocytosis following sulfanilamide administration[12-36] (Fig. 1). Of twenty-seven cases thus collected, fifteen were fatal and twelve recovered. These cases are charted to show the total span of time in days over which sulfanilamide was administered, whether intermittently or continuously, between the day the drug was started and the last dose before agranulocytosis was discovered.

In considering these cases, it is striking that none occurred before the fourteenth day or after the forty-ninth day of therapy, and that all but two occurred within a span of three weeks time. Agranulocytosis developed most often after eighteen to twenty-one days of sulfanilamide therapy. (Agranulocytosis following the use of sulfapyridine or sulfathiazole appears at a similar time.) The dose of sulfanilamide does not seem to be the determining factor in the appearance of agranulocytosis, for while many of the patients received 3 to 6 grams daily, there were several fatal cases that received less than 2 grams a day. Again, agranulocytosis appears at about the same time interval whether the drug has been taken continuously or intermittently. An illustration of this fact appears in the case reported by Alpert and Forbes.[16] This patient

received sulfanilamide for seven days, then was given no more until the sixteenth day, when the drug was administered again for twenty-four hours; on the seventeenth day agranulocytosis was discovered. Whether agranulocytosis would have developed if sulfanilamide had not been given on the sixteenth day is an interesting question; it is not unusual for agranulocytosis to appear several days after the drug has been stopped.

In cases which subsequently develop agranulocytosis, the leucocyte count may remain within the normal range during the first two or three weeks or more of treatment. Thus, Stowell and Button's patient had 5,500 leucocytes on the twenty-sixth day of treatment, three days before sore throat developed; agranulocytosis was first discovered on the thirty-first day, but the exact day of its appearance is uncertain. Likewise, symptoms of toxicity may neither precede nor accompany the development of agranulocytosis, and ulcerative pharyngitis may never appear, even in fatal cases. A number of instances are reported in which the patients felt perfectly well for several days after agranulocytosis was discovered. In other cases, however, there have been fever, rash, vomiting or other toxic symptoms at some time preceding the agranulocytosis. These often occurred in the first week or so of treatment with large doses of sulfanilamide, and later, on a lowered dose, subsided some days before the appearance of the agranulocytosis. Since the same toxic symptoms appear in many more patients who never develop agranulocytosis, it can hardly be said that the one heralds the other. It therefore seems that while injury to the leucocyte forming mechanism may occur within the first two weeks of treatment, such injury is probably followed by a latent period during which it is impossible to foretell the imminence of agranulocytosis. It is during this period that frequent leucocyte counts are of great importance. How much further damage sulfanilamide may do when given after the onset of agranulocytosis remains to be determined; it may be pointed out that McGuire and McGuire's case[33] of agranulocytosis recovered even when the ulcerative pharyngitis was vigorously treated with oral and intravenous sulfonamides.

I have discussed agranulocytosis in detail to show that it appears to represent a sensitivity to sulfanilamide which very infrequently appears during the first few weeks of treatment. How rare it is may be realized when it is considered that this group of fifteen cases includes, with a few unavoidable exceptions, all the fatalities from this cause reported

here and abroad since 1937, while sulfanilamide has been used to treat hundreds of thousands of patients suffering from many kinds of diseases. Once the first weeks of treatment are safely passed, there appears to be no risk of agranulocytosis appearing, as shown by the fact that sulfanilamide has been given to thousands suffering from various chronic infections over periods of months without the report of a single late case. What I have said of agranulocytosis applies even more to other much rarer fatal effects of sulfanilamide which have never been encountered by workers on this particular problem. The risk entailed in giving sulfanilamide seems so much less than the chance of serious rheumatic heart disease developing if treatment is withheld, that I think we must accept that risk and, after proper precautions are taken, disregard it in order to treat the rheumatic patient to the best of our ability. There are, after all, few medical procedures of any therapeutic value which do not entail an element of risk.

Is the use of prophylactic sulfanilamide a practical possibility, or does it necessitate so many laboratory procedures that it can only be carried out in centers of research supported by special funds? Quite properly the initial work on this problem has been carried out with careful laboratory studies, but these were by no means all necessary to safeguard the welfare of the patient, nor to promote the therapeutic value of the undertaking. Antistreptolysin titers, pharyngeal cultures, sedimentation rates and electrocardiographic studies need not be undertaken in the routine care of rheumatic patients in the quiescent stage. It is not even necessary to carry out determinations of the level of sulfanilamide in the blood when the drug is taken in such small amounts, although two or three such determinations may well be done on each patient in the early months of treatment. Total white blood cell counts and hemoglobin determinations are the only routine procedures that must be carried out, and these should be followed carefully during the early weeks of treatment, supplementing them with other blood studies only when these simple blood counts are found to be abnormal. I wish emphatically to differ, therefore, with those who say that prophylactic sulfanilamide can be given with safety only in convalescent homes or specially endowed institutions; such a course would deprive the great majority of rheumatic subjects of the most promising weapon now available to combat rheumatic fever.*

* It remains to be seen whether sulfadiazine will prove equally effective and less toxic than sulfanilamide in this preventive role.

Is it possible to carry out a form of preventive medicine which necessitates the taking of pills every day for years by a person who feels entirely well? Sulfanilamide only gives protection while it is faithfully taken, and rheumatic recrudescences may occur after an interval of years. Since the greater part of the recurrences come within five years of the preceding attack, it would seem that five years would be the shortest span of time the drug should be taken, and for younger children the span should probably be longer. This is a difficult task, but with patience and perseverance in careful case following and education of rheumatic subjects and their parents, I think it can be done on a large scale as well as with a small group. Those individuals who have already had serious encounters with the disease are only too eager to carry out instructions. It is clearly far better to take sulfanilamide prophylactically for years and remain well, than to be forced to take digitalis for years after all chance of recovery is lost.

There are over a million persons in the United States who have suffered from rheumatic fever; 40,000 of them die each year of rheumatic heart disease. In these war years, rheumatic fever is important not only on account of its killing power; it burdens this country in many other ways. The initial phases of rheumatic fever disrupt a child's education by prolonged periods of illness and convalescence, and leave him unfit for the armed forces and for industry on account of organic cardiac lesions. In both the early and terminal phases of this disease long periods of bed care are necessary, involving the prolonged services of physicians and nurses as well as hospital facilities and convalescent homes, which are badly needed for defense purposes. Large sums of money from both public and private funds are expended in caring for victims of this disease and their dependents. The time to inaugurate a program for combatting rheumatic fever with prophylactic sulfanilamide is at hand, and to postpone it until after the war would be to lose sight of the immediate importance of this public health problem.

In this lecture I have pointed out that prophylactic sulfanilamide is effective in preventing rheumatic recrudescences, that it is relatively safe, and that if the routine is stripped to essentials, the cost is far less than the cost of caring for the cardiac invalids these rheumatic subjects would eventually become. An effort should be made to treat every individual who has had rheumatic fever early in the evolution of his disease with *small* daily doses of sulfanilamide and to continue treatment

over a period of years. When this is done, we may hope for real progress in controlling rheumatic heart disease in this country.*

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* I should like to express appreciation to all my associates in the Cardiac Clinic of the Department of Medicine whose interest and coöperation have made this study possible.
The sulfanilamide for these investigations was supplied by the Winthrop Chemical Co., Inc., New York.

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